REMARKS

As an initial matter, Applicants wish to thank the Examiner and her supervisor for granting them an Interview on June 12, 2008 ("the Interview").

Claims 1, 53, 54, 57, 59, 60, and 120-123 are pending in the application. Claims 1, 53, and 59 have been amended and claims 123-131 have been cancelled. Accordingly, claims 1, 53, 54, 57, 59, 60, and 122 will be remain pending in the application upon entry of the claim amendments presented herein.

Support for the Amendments

Support for the amendments is found throughout the specification and claims as originally filed. For example, support for the amendment of claims 1, 53, and 59, which now recite "four to six" and "one to eleven" is found at page 70, line 25, and at page 71, lines 31 and 31, respectively. No new matter has been added.

Amendment and cancellation of the claims here are not to be construed as an acquiescence to any of the rejections/objections made in the instant Office Action or in any previous Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the claims as originally filed, or substantially similar claims in one or more subsequent patent applications.

Election/Restriction

The Examiner asserts that claims 123-131 are directed to non-elected inventions and species. Applicants respectfully disagree with the withdrawal of the claims. However, without acquiescing in any way to the rejection and in order to expedite prosecution of the application, claims 123-131 have been cancelled.

Amendment of Priority Claim

The Examiner has acknowledged that Applicants' application finds support in International Application No. PCT/US98/21168, which claims priority of U.S. 08/946,298, filed on October 7, 1998, now issued as U.S. Patent No. 6,864,060. Applicants have amended their priority information to reflect that this application is the U.S. national stage of International Application No. PCT/US98/21168, filed under 35 U.S.C. § 371, which is a continuation-in-part of USSN 08/946,298, filed on October 7, 1998, now issued as U.S. Patent No. 6,864,060.

Drawings

The Examiner objects to the Drawings for failing to recite Sequence Identifiers for the sequences present at Figure 1. This objection is overcome by the present amendment of the Specification.

Sequence Listing

The Examiner objects to the Sequence Listing for failing to identify the Sequence Identifiers of sequences present at Figure 1. This objection is overcome by the present amendment of the Specification.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 1, 53, 54, 57, 59, 60, and 120-122 are rejected under 35 U.S.C. § 112, first paragraph as lacking enablement in the specification. The claims are directed to yeast cells that contain a heterologous G protein-coupled receptor (GPCR) and a chimeric G protein subunit which contains an endogenous yeast Gpa1 subunit in which the last four to six C-terminal amino acids of Gpa1 are replaced with the last four to six C-terminal amino acids of a first heterologous G protein subunit, and in which the N-terminus of said Gpa1 is linked to the first one to eleven N-terminal amino acids of a second heterologous G protein subunit (claims 1 and 120-122); or in which the last four to six C-terminal amino acids of said Gpa1 are replaced with the last four to six C-terminal amino acids of a first heterologous G protein subunit, and in which the first one to

eleven N-terminal amino acids of said Gpa1 are replaced with the first one to eleven N-terminal amino acids of a second heterologous G protein subunit (claims 53, 54 and 57). Claims 59 and 60 are directed to a chimeric G-protein subunit which comprises an endogenous Gpa1 subunit in which the last four to six C-terminal amino acids of said Gpa1 are replaced with the last four to six C-terminal amino acids of a first heterologous G protein subunit, and in which the N-terminus of said Gpa1 is linked to the first one to eleven N-terminal amino acids of a second heterologous G protein subunit, where the first and second heterologous G protein subunits are the same or different. Such chimeric G protein subunits are termed "sandwich chimeras" because the mammalian amino acid sequences at the amino and carboxy termini of the protein "sandwich" the yeast amino acid sequences between them.

The claims are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner is concerned that the interaction between GPCRs and G proteins is allegedly unpredictable. In support of the alleged unpredictability of the art, during the Interview on June 19, 2008, the Examiner asserted that Applicants' claims read on inoperative embodiments. Applicants respectfully disagree with the rejection, and for the reasons provided below, request that the rejection be withdrawn.

The standard for enablement set forth in 35 U.S.C. 112, first paragraph, requires that Applicants provide a description of the invention sufficient "to enable any person skilled in the art to which it pertains . . .to make and use" the invention. The proper test of enablement is set forth in *United States v. Telectronics, Inc.*, (857 F.2d 778, 785, 8 USPQ2d at 1217, 1223 (Fed. Cir. 1988)):

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation.

The fact that some experimentation may be required to practice the invention does not indicate that the claims lack enablement so long as the experimentation is merely routine. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In Wands, the claims at issue were directed to immunoassays that required the use of monoclonal antibodies. The identification of these antibodies required extensive screening, and the court considered the question of whether undue experimentation would be required to carry out the screens. The

court found that the specification enabled the claims because "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." Id. at 740, 8 USPQ2d at 1406. The Wands court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407.

The present case is analogous to Wands in all important respects because although some screening might be required to identify yeast cells that contain a heterologous G protein-coupled receptor (GPCR) and a chimeric G protein subunit, where expression of the chimeric G protein subunit functionally integrates the heterologous GPCR into the pheromone response pathway of the yeast cell, this screening is merely routine. Moreover, Applicants' specification provides considerable direction and guidance regarding how such screening should be carried out. In particular, at pages 107 to page 108, under the heading "GPA1-Gq sandwich improves functional activity of a bradykinin-responsive receptor" Applicants provide a working example of the claimed yeast cells.

Applicants teach that the GPA1-Gq sandwich chimera increased coupling by the human bradykinin responsive receptor 2 in a functional assay employing β galactosidase as a detectable readout of for receptor coupling. Applicants state "ß galactosidase activities were increased 26-fold in yeast cells transformed with Gαq(1-11)-GPA1(6-467)-Gαq(355-359). . ." Applicants also report coupling to heterologous orphan receptors using G protein sandwich chimeras in the Fus1 p-His3 assay and in the lacZ assay (pages 104-106). Results using the Fus1 p-His3 assay are provided at Table 4, page 105, where Applicants show that the mammalian Bombesin receptor subtype 3 and the Bradykinin receptor 2 functionally coupled to the Gαq(1-11)-GPA1(6-467)-Gαq(355-359) sandwich chimera. Results of the lacZ assay are provided at Table 5, pages 105-106, where Applicants show that mammalian heterologous orphan receptors 11, 15, and 16 also functionally coupled to the Gαq(1-11)-GPA1(6-467)-Gαq(355-359) sandwich chimera. Clearly, Applicants have provided a number of working examples showing that G protein-coupled receptor successfully coupled with GPA1 sandwich chimeras.

Contrary to the Examiner's assertion in the Interview Summary, it is not the state of the art that is predictable, it is the methods that are used to practice the invention that are predictable. One of ordinary skill in the art would be able to make and use the invention commensurate in scope with the claims because all of the methods needed to practice the invention, including methods for making recombinant yeast cells, methods for producing recombinant proteins in yeast, and methods of screening such yeast cells for functional activity, were merely routine and were well known at the time the application was filed as evidenced by the extensive list of references, such as Pausch, Fowlkes, and Conklin, that the Examiner acknowledges describe methods for identifying recombinant yeast cells comprising chimeric G protein subunits (Office action mailed May 17, 2008, page 16, first full paragraph, page 15, fourth full paragraph, and page 22, last paragraph). Thus, the art cited by the Examiner clearly establishes that a skilled artisan could easily produce recombinant Gpa1 subunits, express the chimeric G protein subunits in yeast, and identify those that functionally couple to a heterologous GPCR. Such screening does not constitute undue experimentation because it could easily be accomplished using ***standard*** techniques for generating and screening recombinant yeast cells as described in Applicants' specification, for example, in Example 12, and in the state of the art.

Applicants note that the fact that the screening could be carried out predictably, in no way renders Applicants' discovery predictable. Although the references make clear that the methods required to identify sandwich chimeras were well known, the references uniformly fail to describe the claimed sandwich chimeras, and uniformly fail to indicate that the sandwich chimeras, if made, would function successfully.

In further support of the enablement rejection, the Examiner states:

> . . . it would take "undue experimentation" to screen the numerous possible combinations of GPCRs and chimeric G proteins to determine which combination would produce the working combination and elicit the proper signal transduction activity (Office action mailed May 17, 2007, page 10, third paragraph).

The Examiner asserts that because numerous yeast cells would have to be screened to identify those having the desired characteristics, Applicants have failed to enable the full scope of the claims. This position is contrary to the standard set out by the court in *Wands*. In *Wands*, the

court found that the number of experiments was not determinative of undue experimentation so long as the screening was merely routine. In Wands, 143 hybridomas were screened, and this screening involved "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." Moreover, only 2.8% of the screens identified antibodies having the desired characteristics. Despite the extensive experimental steps required and the large number of antibodies that had to be screened, the court found that the experimentation required was not undue. So too in the present case, even a large amount of screening is not undue because the screening methods are merely routine.

The Examiner further asserts that Applicants have failed to teach "all possible combination of GPCR and Gpa1 (including various mutants) that would produce the proper signal transduction activity." The standard that the Examiner seeks to impose is not found in U.S. patent law. The enablement requirement does not require Applicants to describe all possible combinations falling within the scope of the claims. The U.S. Patent and Trademark Office's training materials are helpful in clarifying this point. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of Section 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." (Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Of Chemical/Biotechnical Applications, § 2.iii.b Reasons For Lack Of Enablement: Undue Experimentation Needed To Make And Use The Invention, http://0-www.uspto.gov.mill1.sjlibrary.org/web/offices/pac/dapp/1pecba.htm#iiia1; emphasis added). The position adopted by the Examiner would apparently seek to limit Applicants to only those working examples set forth in Applicants' specification. The U.S. Patent and Trademark Office's training materials indicate that this is improper. In fact, the training materials caution that the Examiner must be careful not to unduly limit the claims in this fashion.

> In *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated: to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional

> purpose of promoting progress in the useful arts. (Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement OF Chemical/Biotechnical Applications, § III.A.1 *Determining Whether the Enablement Requirement Is Met*, http://0-www.uspto.gov.mill1.sjlibrary.org/web/offices/pac/dapp/1pecba.htm#iiia1; emphasis)

In further support of the enablement requirement, the Examiner asserts that "it is not clear what core sequences are required for the Gpa1 mutants to properly interact with any of the claimed GPCRs." Applicants respectfully disagree. Applicants focus in Example 12 was addressing exactly this issue. Applicants state that "Sandwich chimeric proteins were constructed to investigate the effect on receptor specificity by substituting both the C-terminal and N-terminal regions of the Gpa1 with protein Gα subunits (page 106, lines 8-10)" Applicants construction and characterization of the sandwich chimera Gαq(1-11)-GPA1(6-467)-Gαq(355-359) led to the discovery that replacement of eleven amino acids at one end of the yeast GPA1 subunit (e.g., Gαq(1-11)) and five amino acids at the other end (e.g., Gαq(355-359)) resulted in receptor coupling (Table 4, p. 105, and Table 5, p. 105).

In fact, not only was functional coupling observed, but Applicants discovered that the sandwich chimeras unexpectedly increased the functional activity of the mammalian bradykinin-responsive receptor when that heterologous G protein coupled receptor was expressed in yeast (page 107, line 33, to page 108, line 15). Thus, contrary to the Examiner's assertion, Applicants have clearly identified those terminal regions where replacement of the C-terminal and N-terminal amino acids of the Gpa1 with protein Gα subunit sequences enhanced interaction with heterologous G protein coupled receptors. Moreover, Applicants have provided extensive guidance regarding those amino acids at each termini that should be replaced (page 69, under the heading "Sandwich" Chimera G Proteins).

In further support of the enablement rejection, the Examiner asserts that Applicants' claims read on inoperative embodiments. During the Interview, the Examiner specifically pointed to Table 3 as including a number of inoperative embodiments. Applicants note that the chimeric G subunits analyzed in Table 3 do not fall within the scope of Applicants claims because they are not sandwich chimeras, i.e., they do not include heterologous sequences at both the N and C termini. As detailed above, results with sandwich chimeras are described at Tables

4 and 5. Nevertheless, even if we assume i*n arguendo* that Applicants claims do embrace one or more inoperative embodiments, the mere presence of such inoperative embodiments within the scope of a claim does not demonstrate that the claim lacks enablement. Applicants welcome the Examiner's attention to the U.S. Patent and Trademark Office's Training Materials, which is helpful in clarifying this point. "The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. duPont de Nemous & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement OF Chemical/Biotechnical Applications, § 2. Inoperability/Inoperative Species within the Scope of the Claim, http://0-www.uspto.gov.mill1.sjlibrary.org/web/offices/pac/dapp/1pecba.htm#iiia1).

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 1, 53, 54, 57, 59, 60, and 120-122 are rejected under 35 U.S.C. 112, second paragraph for alleged indefiniteness. Further to the Interview, Applicants' understand that the rejection of the claims as lacking antecedent bases is withdrawn. Applicants respectfully disagree with the remaining rejection for indefiniteness. However, without acquiescing in any way to the rejection and in order to expedite prosecution of the application, claims 1, 53, and 59, from which the remaining rejected claims depend, have been amended, thereby obviating the rejection. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 59, 121, and 122 are rejected as allegedly anticipated by Pausch (WO 95/21925; hereinafter "Pausch"); and claims 1, 53, 59, and 120-122 are rejected as allegedly anticipated by Fowlkes (WO 94/23025; hereinafter "Fowlkes"). Applicants respectfully disagree with the rejection, and for the reasons discussed below request that it be withdrawn.

As discussed with the Examiner in the Interview, Pausch fails to describe a chimeric G protein subunit having amino acids replaced at both the amino and carboxy termini. Accordingly, the rejection over Pausch should be withdrawn.

Fowlkes describes chimeric Gα subunits where at least 20 or 40 amino acids at the amino terminus of Gα are replaced and 10 or 20 amino acids at the carboxy terminus are replaced. Fowlkes fails to teach that as few as four amino acids at the carboxy terminus and as few as one to eleven amino acids at the amino terminus can be replaced, as recited in Applicants' claims. Because Fowlkes fails to teach each and every element of Applicants claims, Fowlkes fails to anticipate Applicants' claims. Accordingly, the anticipation rejection over Fowlkes should also be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 53, 54, 57, 59, 60, and 120-122 are rejected for obviousness.

Claims 1, 57, 59, 121, and 122 are rejected over Pausch and Conklin (*Molec. Pharm.* 50:885-890, 2004; hereinafter "Conklin");

Claims 1, 57, 59, 121, and 122 are further rejected over Pausch, Conklin, and Fowlkes;

Claims 1, 53, 57, 59 and 120-122 are further rejected over Fowlkes and Conklin;

Claims 1, 53, 54, 57, 59, 60, and 120-122 are further rejected over Pausch, Conklin, and Fowlkes in view of Hamm (*J. Biol. Chem* 273:669-672, 1998; hereinafter "Hamm"). Applicants respectfully disagree.

The test of obviousness requires that one compare the claimed "subject matter as a whole" with the prior art "to which said subject matter pertains" 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three criteria must be met. First, a suggestion or motivation to modify the reference or combine reference teachings must be present in the references or in the general knowledge present in the art. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. M.P.E.P. 2143. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons skilled in the art." *In re Rouffet*, 149 F.3d 1350, 1357. In the absence of

some teaching or suggestion to combine, no *prima facie* case of obviousness can be established, and the rejection is improper and must be withdrawn. *In re Fine*, 837 F.2d 1071, 1074.

In the present case, the references cited by the Examiner fail to provide the requisite motivation to combine; fail to provide a reasonable expectation of success; and fail to teach or suggest all of the claim limitations.

Pausch and Conklin

Claims 1, 57, 59, 121, and 122 are rejected as obvious over Pausch and Conklin. The claims are directed to yeast cells comprising chimeric Gα subunits having heterologous amino acids at both the C and N termini.

As discussed during the Interview, Pausch fails to describe the replacement of amino acids at the C terminus as recited in Applicants' claims. To remedy this deficiency, the Examiner cites Conklin.

Conklin describes mutations of the **carboxyl-terminal of the G-protein α subunit.** Neither Pausch nor Conklin teaches or suggests modifying the N-terminus portion of GPA-1. In the absence of such a teaching or suggestion, one of skill in the art would lack the requisite motivation to introduce a change at the N-terminus, and would lack the expectation that such a change would successfully couple with a heterologous G protein coupled receptor. Accordingly, the obviousness rejection of the claims over Pausch and Conklin should be withdrawn.

Pausch, Conklin, and Fowlkes

Claims 1, 57, 59, 121, and 122 are rejected over Pausch and Conklin in view of Fowlkes. As detailed above, and as discussed in the Interview, Pausch and Conklin fail to teach or suggest any modification at the N-terminus of a Gpa1 subunit, much less the specific modifications recited in Applicants' claims. The Examiner cites Fowlkes to remedy the deficiencies of Pausch and Conklin.

As detailed above, Fowlkes fails to teach or suggest chimeric G proteins, where the N-terminus of Gpa1 is coupled to as few as the first one to eleven N-terminal amino acids of a second heterologous G protein subunit as recited in the claims. In contrast to Applicants' claims, Fowlkes teaches that at least 20 or 40 N-terminal amino acids should be replaced. Practice of

Applicants' claimed invention would not infringe the methods described by Fowlkes. Thus, Fowlkes fails to anticipate Applicants claims. This principle is embodied in the following maxim: "That which infringes if later anticipates if earlier." Polaroid Corp. v. Eastman Kodak Co., 789 F.2d 1556, 1573, 229 USPQ 561, 574 (Fed. Cir. 1986). Fowlkes failed to recognize, as Applicants did, that replacement of as few as the first one to eleven N-terminal amino acids would be sufficient to enhance coupling.

Applicants were the first to discover that sandwich chimeras could functionally couple to a chimeric G protein coupled receptor. Because Fowlkes failed to make or analyze a single chimeric G protein having substitutions at both the amino and carboxy termini Fowlkes could not know whether or not such a protein would function successfully. In the absence of a teaching that a sandwich chimera would successfully couple with a heterologous G protein coupled receptor, one of skill in the art would lack the necessary expectation of success to make the specific modifications claimed by Applicants. Thus, the rejection of the claims over Pausch and Conklin in view of Fowlkes should also be withdrawn.

Pausch, Conklin, Fowlkes, and Hamm

Claims 1, 53, 54, 57, 59, 60, and 120-122 are rejected under 35 U.S.C. § 103(a) over Pausch, Conklin, and Fowlkes, in view of Hamm. None of the foregoing references describes each and every limitation of Applicants' claimed invention, and none provides the requisite motivation to modify the N-terminus of Gpa1. The Examiner relies on Hamm to supply the motivation that is uniformly missing in the foregoing references. The Examiner asserts that Hamm teaches that the N-terminus of the alpha G-protein subunit appears to be involved in promoting heterologous receptor contact. In particular, the Examiner asserts that Hamm proposes that modifications should be made in the C-terminal and N-terminal regions of Gα subunits. Applicants respectfully disagree.

Hamm provides a review of G protein structure and the mechanism of activation of G proteins by receptors. Hamm fails to suggest that any experiments should be conducted to determine the effects of mutating a Gpa1 subunit on functional coupling in a yeast cell, much less the specific mutations recited in Applicants' claims. Although Hamm acknowledges that the

N-terminal region of Gα is "implicated" in receptor contact (page 669, right column, 4th paragraph), Hamm states:

> On the α subunit, ***the best characterized receptor contact region is at the C terminus***. The last 7 amino acids of the α subunit are disordered in the heterotrimer crystal structures, and analysis of receptor-binding peptides selected from a combinatorial peptide library shows that ***these 7 residues are the most critical***. Studies using chimeric Gα subunits confirm that in fact ***the last 5 residues contribute importantly to specificity of receptor G protein interaction***. Elegant mutagenesis studies have shown that the C terminus of the third intracellular loop of receptors binds to ***this C-terminal region on Gα subunits***. (p. 669, third paragraph, Emphasis added.)

By emphasizing the importance of the C terminus in mediating receptor contact and specificity, Hamm and the other cited references not only direct the skilled artisan's attention towards the C terminus, they teach away from modifying the N terminus of the protein. In the absence of a suggestion that modified subunits ***should be made***, and if made, that such subunits would function successfully, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, the obviousness rejection is improper and should be withdrawn.

Rejections for nonstatutory obviousness-type double patenting

Claims 1, 53, 59, and 120-122, which are directed to yeast cells that contain a heterologous G protein-coupled receptor (GPCR) and a chimeric G protein subunit, are rejected for nonstatutory obviousness-type double patenting over claims 1-4 of U.S. Patent No. 6,864,060 in view of Fowlkes (WO 94/23025). Applicants respectfully disagree and traverse the rejection.

Applicants note that they will file a terminal disclaimer, if appropriate, once otherwise allowable subject matter has been determined in the present application.

CONCLUSION

In view of the above remarks, Applicants believes the pending application is in condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be allowable, Applicants respectfully request the Examiner to telephone Applicants' undersigned representative at the number below so that a telephonic interview may be scheduled. Applicants thank the Examiner in advance for this courtesy.

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Respectfully submitted,

By 

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